

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of:
Brockhaus et al.

Application No.: 08/444,791

Art Unit: 1644

Filed: May 19, 1995

Examiner: R. Schwadron

For: HUMAN TNF RECEPTOR

DECLARATION OF STEWART LYMAN, PH.D. UNDER 37 C.F.R 1.132

1. I received a Ph.D. in Oncology from the McArdle Laboratory for Cancer Research at the University of Wisconsin-Madison in 1984. I did postdoctoral research at the Fred Hutchinson Cancer Research Center in Seattle, and joined Immunex Corporation as a molecular biologist in 1988. I was a scientist at Immunex Corporation for 14 years, eventually becoming Director of Extramural Research. After Amgen acquired Immunex in 2002, I stayed on and worked for Amgen for three months in a transitional role. Since 2004, I have managed my own consulting business, and I am being compensated for my time consulting on this matter at my usual hourly rate. I also own 100 shares of Amgen stock. My Curriculum Vitae is attached as Exhibit A.
2. I have reviewed the above-identified application as originally filed. I have been informed that the effective filing date of the above-identified application is August 31, 1990. In particular I have reviewed page 9, line 19 to page 10, line 10 of the application, which refers to Smith *et al*, *Science* 248: 1019-1023, 1990 (referred to hereafter as “Smith (1990)”):

In addition thereto, the present invention is also concerned with DNA sequences coding for proteins and soluble or non-soluble fragments thereof, which bind TNF. Thereunder there are to be understood, for example, DNA sequences coding for non-soluble proteins or soluble as well as non-soluble fragments thereof, which bind TNF, such DNA sequences being selected from the following:

- (a) DNA sequences as given Figure 1 or Figure 4 as well as their complementary strands, or those which include these sequences;
- (b) DNA sequences which hybridize with sequences defined under (a) or fragments thereof;
- (c) DNA sequences which, because of the degeneracy of the genetic code, do not hybridize with sequences as defined under (a) and (b), but which code for polypeptides having exactly the same amino acid sequence.

That is to say, the present invention embraces not only allelic variants, but also those DNA sequences which result from deletions, substitutions and additions from one or more nucleotides of the sequences given in Figure 1 or Figure 4, whereby in the case of the proteins coded thereby there come into consideration, just as before, TNF-BP [TNF binding proteins]. One sequence which results from such a deletion is described, for example, in [Smith et al.,] Science 248, 1019-1023, (1990).

3. I have been informed that the Patent Office has objected to the amendment to the specification which inserts the phrase "incorporated by reference" with respect to the sequence provided in Smith (1990), because this insertion introduces new matter into the application. I have reviewed page 2 of the Office Action dated June 8, 2010 which sets out this objection and make this declaration to address the objection.
4. I have been informed that the standard for properly incorporating material by reference into a patent application is that the application clearly identifies the reference publication and the application must clearly convey an intent to incorporate the material by reference.

5. I believe that I am qualified by my education and training to attest to what one skilled in the art would have understood from reading the application as of August 31, 1990. In 1990, I was well experienced in the molecular biology of type I transmembrane receptors. For example, we had recently cloned and expressed the c-kit tyrosine kinase receptor protein, a type I transmembrane receptor (Williams et al., Cell, 63, 167-174, 1990). In addition, I had worked on elucidating the relationship between the IL-4 receptor (also a type I transmembrane receptor) and other cytokine receptors. (Cosman et al., Trends in Biol. Sci. 15:265-270, 1990) The extracellular, ligand-binding domain of the IL-4 receptor showed homology to several other cytokine receptors. This homology allowed us to define a new class of cytokine receptors. Starting in 1988, I also initiated a project at Immunex that resulted in the cloning of a number of cell surface receptors and their ligands. During the course of this work, I had occasion to make DNA constructs encoding soluble forms of type I transmembrane receptors (i.e., not membrane bound) as well as insoluble chimeric receptors containing the extracellular domain of one receptor fused to the transmembrane and cytoplasmic domains of a different receptor.
6. I note the following points as background to the discussion below. I read the application as being concerned with two tumor necrosis factor binding proteins ("TNF-BP"), one about 55 kD in size and one about 75 kD in size. The application's discussion of these two TNF binding proteins is consistent with what was known in the art as of August 31, 1990, i.e. that there were two membrane bound TNF receptors (TNFR) of approximately these sizes. The former is also

variously referenced in the literature as TNFR I, 55 kd TNFR, or p55 TNFR. The latter is also variously referenced in the literature as TNFR II, 75 kd TNFR, or p80 TNFR.

7. Figure 4 of the application displays a partial nucleotide and amino acid sequence corresponding to the p75 TNFR.
8. There is a description in the application of the specific full length sequence of the 75 kd TNFR. It is clear from the citation to the Smith (1990) article at page 10, lines 9-10 of the application that the Applicants knew of the Smith (1990) article when they drafted the application and intended to refer to its sequence.
9. It is disclosed in the application (page 35, lines 22-33) that Figure 4 is a partial cDNA sequence. Since the amino acid sequence of Figure 4 is almost identical (almost 99% identical) to that of Smith (1990), it would be clear to one of skill in the art that the sequence of Figure 4 was a partial sequence of the same protein described in Smith (1990). Attached as Exhibit B is an alignment of the Figure 4 sequence with part of the Smith (1990) sequence of p75 TNFR to illustrate this point. Further, the disclosure (page 33, lines 7-19) of the following 18-mer as the amino terminal peptide of a protein detected as a 65/75 kD band was also consistent with this conclusion because the 18-mer matches exactly the mature amino terminus of p75 as disclosed in Smith (1990), save for one amino acid, the identity of which was not determined:

Leu-Pro-Ala-Gln-Val-Ala-Phe-X-Pro-Tyr-Ala-Pro-Glu-Pro-Gly-Ser-Thr-Cys.

10. When the entirety of the quote in paragraph 2 above is read, one sees that the paragraph refers to soluble and non-soluble fragments of TNF binding proteins,

i.e. the TNF receptors described in the application. Thus, one of skill in the art would have concluded that the citation to Smith (1990) was a reference to whatever soluble or non-soluble fragments of TNF binding proteins were described in the article. Despite differences between the sequences disclosed in the application and those in the Smith (1990) article, the amino acid sequences are nearly 99% identical overall. I would interpret the quote in paragraph 2 above to mean that the Smith sequence was contemplated by the inventors because the Smith (1990) article is specifically cited.

11. One of skill in the art would not have read the application by itself without reference to any other known information. Instead, such a person would have read the application in view of what was known in the art at the effective filing date, particularly in view of the following statements in the application:

“the present invention embraces . . . One sequence which results from such a deletion is described, for example, in [Smith et al.,] Science 248, 1019-1023, (1990).”

Specification, page 10, lines 3-10. One of skill in the art would also have noted that Dembic *et al. Cytokine* 2(4): 231-7, 1990, published by the same authors as the inventors on the application, disclosed the entire sequence of the mature 75 kD TNFR, which was the same sequence as in Smith (1990), and the same extracellular region (page 232 to page 233, upper left column; and Figure 1 at page 232). Thus, one of skill in the art would have had no doubt that the inventors were in possession of the entire p75 sequence as of August 31, 1990 and that the Applicants clearly intended to incorporate the entire p75 amino acid sequence into the specification.

12. For all of these reasons, it is clearly indicated in the specification that the skilled artisan should look to the Smith (1990) article as a source of information about sequences of soluble fragments of the TNF-BP that can be used.
13. The citation includes the journal name, journal volume, page numbers and year, and thus is a complete citation that uniquely identifies the article. Figure 3 of Smith (1990) discloses the only TNF receptor sequence in this publication, from among the p55 or p75 TNF receptors that are the subject of the application. Thus, the application clearly identifies the reference publication and the application clearly conveys an intent to incorporate by reference the sequences in Smith (1990) of soluble or non-soluble TNF receptors.
14. I further declare that all statements made herein of my own knowledge are true, that all statements made on information and belief are believed to be true, and that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both (18 U.S.C. § 1001), and may jeopardize the validity of the application or any patent issuing thereon.

Dated: Sept. 3, 2010

Stewart Syman

EXHIBIT A**CURRICULUM VITAE**

NAME: Stewart David Lyman

PRESENT POSITION: Manager, Lyman BioPharma Consulting LLC

HOME ADDRESS: 1836 N. 53rd St. Seattle, WA 98103

E-MAIL ADDRESS: stewartlyman@comcast.net

TELEPHONE: (206) 632-2188 (Home)
(206) 931-6403 (Work)

PLACE OF BIRTH: New Rochelle, NY

EDUCATION:

<u>Degree</u>	<u>Institution</u>	<u>Discipline</u>
B.S. (Magna cum laude)	State University of New York at Albany, Albany, NY	Biology
Ph.D.	McArdle Laboratory for Cancer Research University of Wisconsin Madison, WI	Oncology
Dissertation:	"Genetic and Metabolic Factors that May Affect the Biological Activity of Xenobiotics in Mice"	

EMPLOYMENT HISTORY:

2003 – present: Manager, Lyman BioPharma Consulting LLC

1988-2002: Immunex Corporation:

1999-2002: Director, Extramural Research

1993-1999: Senior Staff Scientist

1988-1992: Staff Scientist

Project Chair, creator of the Receptors in Search of Ligands (RISOL) Project, 1989-1994. Receptors used as tools to clone novel ligands.

Project Chair of the Signal Transduction Project, 1990-1991.

Project Chair of the Flt3 Ligand Development Project, 1994-1996.

Project Co-Chair of the Expressed Sequence Tag Project, 1995-1996.

Project Co-Chair of the Core Pipeline Technology Project, 1997-1999.

Project Co-Chair of the Basic Biology Project, 1999.

1984-1988: Post-doctoral Fellow: Fred Hutchinson Cancer Research Center, Seattle, WA. Laboratory of Dr. Larry Rohrschneider. Studied the mechanism of cellular transformation by the *v-fms* oncogene.

PROFESSIONAL ASSOCIATIONS:

American Association for the Advancement of Science

RESEARCH INTERESTS:

Identification of novel growth factors; role of growth factors in development of the hematopoietic and immune systems, role of growth factors in oncology.

HONORS AND AWARDS:

Regents Scholarship, SUNY Albany, 1973-1977
Biological Honor Society, SUNY Albany, 1976-1977
Danforth Fellowship nominee, SUNY Albany, 1977
U.S. Public Health Service National Research Service Award
McArdle Laboratory for Cancer Research, 1977-1982
NIH Postdoctoral Training Grant in Viral Oncology
University of Washington, January-September 1985
Individual National Research Service Award,
National Cancer Institute, October 1985-December, 1987.
Visiting Scientist Fellowship, Molecular Biology Computer Research
Resource, Dana-Farber Cancer Institute, Boston, MA; December 1986

ADVISORY BOARDS:

Advisory Board Member "Modern Drug Discovery", 1998 - 2004.

AWARDED PATENTS AND PATENT APPLICATION FILINGS:

U.S. Patent #5,512,457 – Cytokine designated Elk ligand
U.S. Patent #5,627,267 – Cytokine designated Elk ligand
U.S. Patent #5,670,625 – Elk ligand fusion proteins
U.S. Patent #5,728,813 – Antibodies directed against Elk ligand
U.S. Patent #5,554,512 – Ligands for Flt3 receptors
U.S. Patent #5,843,423 – Flt3 ligand stimulation of hematopoietic cells
U.S. Patent #6,190,655 – Flt3 ligand uses for exogenous gene transfer
U.S. Patent #6,540,992 – Methods for using elk-L to enhance neuronal survival
U.S. Patent #6,555,520 – Human TSLP DNA and polypeptides
U.S. Patent #6,630,143 – Antibodies against flt3 ligand
U.S. Patent #6,632,424 – Human flt3 ligand
U.S. Patent #6,762,030 – Ligand for CD7, and methods for use thereof
U.S. Patent #6,919,206 – Medium containing flt3 ligand for culturing hematopoietic cells
U.S. Patent #6,994,989 – FLK-1 binding proteins
U.S. Patent #7,041,282 – Ligands for flt3 receptors
U.S. Patent #7,045,128 – Antibodies against flt3 ligand

WO 92/00376 – The *c-kit* ligand (Steel factor)

WO 97/17442 – Novel VEGF related ligand for flk-1/KDR receptor

WO 99/33984 – V197 Polypeptide
WO 99/33983 – V201 Polypeptide
WO 99/33877 – V196 Polypeptide

INVITED TALKS AT MEETINGS:

Biology of IL-4 Receptor:

FASEB conference on Receptors, June 1990

Biotechnological Applications in the 1990's, UC-Irvine, Irvine, CA, May 1990

Biology of Steel Factor (c-kit Ligand):

Armand Hammer Workshop: Regulation of Hematopoietic Stem Cells, La Jolla, CA, October 1990

Nargis Dutt Memorial Symposium: Cytokines in Clinical Medicine, UC-Irvine, Irvine CA
October 1990

Stromal Regulation of Hematopoiesis, Bethesda, MD, June 1991

Blood Cell Growth Factors Meeting, Beijing, China, August 1991

American Society for Pediatric Hematology/Oncology, Chicago IL, September 1991

AACR 43rd Annual Symposium on Fundamental Cancer Research: "Growth Factors and their
Receptors in Cancer: Basic Mechanisms and Therapy" Houston, Texas, November 1991

Biology of Flt3 Ligand:

Plenary Session, 1993 ASH meeting, St. Louis, MO. December, 1993

Keystone Hematopoiesis Conference, Breckenridge, CO January, 1994

Advances in Bone Marrow Transplantation, Valhalla, NY March 7, 1994

Advances in Hematopoiesis Conference, Tokyo, Japan July 1994

The Metcalf Forum: Polyfunctionality of Hematopoietic Regulators, Dublin, Ireland September
1994

Mehdi Tavissoli Memorial Symposium: Hematopoietic Stem Cells, Reno, Nevada, November 1994

Taniguchi Foundation Symposium: Regulation of Hematopoietic Stem Cells, Osaka, Japan, December
1994

9th Symposium, Molecular Biology of Hematopoiesis, Genoa, Italy, June 24-27, 1995

International Society for Experimental Hematology, Dusseldorf, Germany, August 26-31, 1995

International Symposium on Bone Marrow Transplantation: Basic and Clinical Studies, Tokyo, Japan,
October 9-10, 1995

American Association for Cancer Research Satellite Symposium: Cytokines and Cytokine Receptors,
Lake George, NY, October 1995

Southern Blood Club, New Orleans, LA, February 1, 1996

Wilsede Conference, Human Leukemia Meeting, Hamburg, Germany, June 14-18, 1996

Research Trends in Hematopoietic Cell Culture, Tokyo, Japan, August 26-28, 1996

Biological Therapy of Cancer, Munich, Germany, June 11-14, 1997

IBC conference "Hematopoietic Stem Cells" San Diego, CA, June 23-24, 1997

International Society for Experimental Hematology, Cannes, France, August 24-28, 1997

Mini-symposium: Tyrosine kinase receptors, University of Lund, Sweden, August 29, 1997

PUBLICATIONS (Abstracts not included):

1. **Lyman, S.D.,** Poland, A., and Taylor, B.A. Genetic polymorphism of microsomal epoxide hydrolase activity in the mouse. J. Biol. Chem. 255, 8650-8654, 1980.

2. **Lyman, S.D.**, and Poland, A. Effect of the brachymorphic trait in mice on xenobiotic sulfate ester formation. *Biochem. Pharm.* 32, 3345-3350, 1983.
3. Jordan, V.C., Bain, R.R., **Lyman, S.D.**, and Brown, R.R. Analysis of Tamoxifen and its metabolites. In: Drug Determination in Therapeutic and Forensic Context, Ed. by E. Reid and I.D. Wilson, Plenum Press, p. 219-225, 1984.
4. **Lyman, S.D.**, and Jordan, V.C. Antiestrogenic effect of trifluoperazine in mice. *Biochem. Pharmacol.* 34, 2221-2224, 1985.
5. **Lyman, S.D.**, and Jordan, V.C. Metabolism of Tamoxifen and its uterotrophic activity. *Biochem. Pharmacol.* 34, 2787-2794, 1985.
6. **Lyman, S.D.**, and Jordan, V.C. Possible mechanisms for the agonist actions of Tamoxifen and the antagonist actions of MER-25 (Ethamoxytriphetol) in the mouse uterus. *Biochem. Pharmacol.* 34, 2795-2806, 1985.
7. Jordan, V.C., Tate, A.C., **Lyman, S.D.**, Gosden, B., Wolf, M.F., Bain, R.R., and Welshons, W.V. Rat uterine growth and induction of progesterone receptor without estrogen receptor translocation. *Endocrinology* 116, 1845-1857, 1985.
8. **Lyman, S.D.**, and Jordan, V.C. Metabolism of non-steroidal antiestrogens, In: Estrogen and Antiestrogen Action (V.C. Jordan, Ed.), University of Wisconsin Press, Madison, WI, pp. 191-219, 1986.
9. **Lyman, S.D.**, and Rohrschneider, L.R. Analysis of functional domains of the *v-fms* encoded protein of feline sarcoma virus by linker insertion mutagenesis. *Molecular and Cellular Biology* 7, 3287-3296, 1987.
10. **Lyman, S.D.**, Park, L. and Rohrschneider, L.R. Colony stimulating factor-1 induced growth stimulation of *v-fms* transformed fibroblasts. *Oncogene* 3, 391-395, 1988.
11. **Lyman, S.D.** and Rohrschneider, L.R. The kinase activity of the *v-fms* encoded protein has a low pH optimum. *Oncogene Research* 4, 149-155, 1989.
12. Idzerda, R.L., March, C.J., Mosley, B., **Lyman, S.D.**, VandenBos, T., Gimpel, S.D., Din, W.S., Grabstein, K.H., Widmer, M.B., Park, L.S., Cosman, D., and Beckmann, M.P. Human interleukin-4 receptor confers biological responsiveness and defines a novel receptor superfamily. *J. Exp. Med.* 171, 861-873, 1990.
13. Beckmann, P.M., Cosman, D., Mosley, B., Maliszewski, C.R., **Lyman, S.D.**, March, C.J., Park, L.S., and Idzerda, R.L. Characterization of the interleukin-4 receptor: A member of the hematopoietin receptor superfamily, in Molecular and Cellular Biology of Cytokines Oppenheim, Powanda, Kluger, and Dinarello, Eds. Wiley-Liss, Inc. pp. 161-166, 1990.
14. Cosman, D., **Lyman, S.D.**, Idzerda, R.L., Beckmann, M.P., Park, L.S., Goodwin, R.G., and March, C.J. A new cytokine receptor superfamily. *Trends in Biol. Sci.* 15: 265-270, 1990.

15. Williams, D. E., Eisenman, J., Baird, A., Rauch, C., Van Ness, K., March, C.J., Park, L.S., Martin, U., Mochizuki, D.Y., Boswell, H. S., Burgess, G. S., Cosman, D., and **Lyman, S.D.** Identification of a ligand for the *c-kit* proto-oncogene. *Cell*, 63, 167-174, 1990.
16. Copeland, N.G., Gilbert, D.J., Cho, B.C., Donovan, P.J., Jenkins, N.A., Cosman, D., Anderson, D., **Lyman, S.D.**, and Williams, D.E. Mast cell growth factor maps near the steel locus on mouse chromosome 10 and is deleted in a number of steel alleles. *Cell* 63, 175-183, 1990.
17. Anderson, D. M., **Lyman, S. D.**, Baird, A., Wignall, J.M., Eisenman, J., Rauch, C., March, C.J., Boswell, H. S., Gimpel, S.D., Cosman, D., and Williams, D. E. Molecular cloning of mast cell growth factor, a hematopoietin that is active in both membrane bound and soluble forms. *Cell* 63, 235-243, 1990.
18. Broxmeyer, H.E., Cooper, S., Lu, L., Hangoc, G., Anderson, D., Cosman, D. **Lyman, S.D.**, and Williams, D.E. Effect of murine mast cell growth factor (*c-kit* proto-oncogene ligand) on colony formation by human marrow hematopoietic progenitor cells. *Blood* 77, 2142-2149, 1991.
19. Broxmeyer, H.E., Hangoc, G., Cooper, S., Anderson, D., Cosman, D., **Lyman, S.D.**, and Williams, D.E. Influence of murine mast cell growth factor (*c-kit* ligand) on colony formation by mouse marrow hematopoietic progenitor cells. *Exp. Hematol.* 19, 143-146, 1991.
20. Brannan, C.I., **Lyman, S.D.**, Williams, D.E., Eisenman, J., Anderson, D.M., Cosman, D., Bedell, M. A., Jenkins, N. A., and Copeland, N. G. Steel-Dickie mutation encodes *c-kit* ligand lacking transmembrane and cytoplasmic domains. *Proc. Natl. Acad. Sci.* 88, 4671-4674, 1991.
21. Keshet, E., **Lyman, S.D.**, Williams, D.E., Anderson, D.M., Jenkins, N. A., Copeland, N. G., and Parada, L.F. Embryonic RNA expression patterns of the *c-kit* receptor and its cognate ligand suggest multiple functional roles in mouse development. *EMBO J.* 10, 2425-2435, 1991.
22. Beckmann, M. P., Cosman, D., Fanslow, W., Maliszewski, C. R., and **Lyman, S. D.** The Interleukin-4 receptor: Structure, function, and signal transduction. in Interleukins: Molecular Biology and Immunology. Chemical Immunology, T. Kishimoto (Ed.) Basel, Karger, 1992.
23. Miller, B.A., Perrine, S. P., Bernstein, A., **Lyman, S.D.**, Williams, D.E., Bell, L. L., and Olivieri, N. Influence of Steel factor on hemoglobin synthesis in sickle cell disease. *Blood* 79, 1861-1868, 1992.
24. Wang, C., Koistinen, P., Yang, G.S., Williams, D.E., **Lyman, S.D.**, Minden, M.D., and McCulloch, E. A. Mast cell growth factor, the ligand for the receptor encoded by *c-kit*, effects the growth and ara-C sensitivity of the blast cells of acute myeloblastic leukemia. *Leukemia* 5, 493-499, 1991.
25. Koistinen, P., Wang, C., Yang, G.S., Wang, Y.-F., Curtis, J.E., Williams, D.E., **Lyman, S.D.**, Minden, M.D., and McCulloch, E.A. OCI/AML-4, an acute myeloblastic leukemia cell line: Regulation and response to cytosine arabinoside. *Leukemia* 5, 704-711, 1991.
26. Williams, D.E., Anderson, D.M., and **Lyman, S.D.** Identification and characterization of a ligand for the *c-kit* proto-oncogene. The Regulation of Hemoglobin Switching. Proceedings of the 7th Meeting on Hemoglobin Switching. G. Stamatoyannopoulos and A. Nienhuis, Eds. Johns Hopkins University Press, Baltimore, MD. pp. 454-459, 1991.

27. Rottapel, R., Reedijk, M., Williams, D.E., **Lyman, S.D.**, Anderson, D. M., Pawson, T., and Bernstein, A. The Steel/W signal transduction pathway: Kit autophosphorylation and its association with a unique subset of cytoplasmic signaling proteins is induced by the Steel factor. *Mol. Cell. Biol.* 11, 3043-3051, 1991.
28. Anderson, D., Williams, D. E., Tushinski, R., Gimpel, S., Eisenman, J., Cannizzaro, L.A., Aronson, M, Croce, C.M, Huebner, K., Cosman, D. and **Lyman, S.D.** Alternate splicing of mRNAs encoding human mast cell growth factor and localization of the gene to chromosome 12q22-24. *Cell Growth and Differentiation* 2, 373-378, 1991.
29. Reith, A.D., Ellis, C., **Lyman, S.D.**, Anderson, D.M., Williams, D.E., Bernstein, A., and Pawson, T. Signal transduction by normal isoforms and W mutant variants of the kit receptor tyrosine kinase. *EMBO J.*, 10, 2451-2459, 1991.
30. Funasaka, Y, Boulton, T., Cobb, M., Yarden, Y., Fan, B., **Lyman, S. D.**, Williams, D. E., Anderson, D. M., Zakut, R., Mishima, Y., and Halaban, R. c-kit kinase induces a cascade of protein tyrosine phosphorylation in normal human melanocytes in response to mast cell growth factor and stimulates mitogen activated protein kinase but is down-regulated in melanomas. *Mol. Biol. Cell* 3, 197-209, 1992.
31. Olivieri, N. F., Grunberger, T., Ben-David, Y., Ng, J., Williams, D. E., **Lyman, S. D.**, Anderson, D. M., Axelrad, A.A., Correa, P., Bernstein, A., and Freedman, M. H. Diamond-Blackfan anemia: Heterogenous response of hematopoietic progenitor cells in vitro to the protein product of the *Steel* locus. *Blood* 78, 2211-2215, 1991.
32. Williams, D.E., Fletcher, F.A., **Lyman, S.D.**, and de Vries, P. Cytokine regulation of hematopoietic stem cells. *Seminars in Immunology* 3, 391-396, 1991.
33. Dolci, S., Williams, D.E., Ernst, M. K., Resnick, J. L., Brannan, C.I., Lock, L.F., **Lyman, S.D.**, Boswell, H. S. and Donovan, P. J. Requirement for mast cell growth factor for primordial germ cell survival in culture. *Nature* 352, 809-911, 1991.
34. **Lyman, S. D.** and Williams, D. E. Alternate splicing of mRNAs that encode mast cell growth factor and the c-*kit* proto-oncogene: Potential effects on protein interactions, pp. 183-193, in Blood Cell Growth Factors: Their Present and Future Use in Hematology and Oncology. Martin Murphy, Jr., (Ed.), Alpha Med Press , Dayton, OH 1991.
35. Williams, D. E. and **Lyman, S. D.** Characterization of the gene-product of the Steel locus. *Progress in Growth Factor Research* 3, 235-242, 1991.
36. **Lyman, S. D.** and Williams, D. E. Biological activities and potential therapeutic uses of Steel factor: A new growth factor active on multiple hematopoietic lineages. *Amer. J. Pediatr. Hematol. Oncol.* 14, 1-7, 1992.
37. Williams, D. E., Foxworthe, D., Teepe, M., **Lyman, S. D.**, Anderson, D., and Eisenman, J. Recombinant murine steel factor stimulates in vitro production of Granulocyte-Macrophage progenitor cells. *J. Cell. Biochem.* 50, 221-226, 1992.

38. Murphy, M., Reid, K., Williams, D. E., **Lyman, S. D.**, and Bartlett, P. F. Steel factor is required for maintenance, but not differentiation, of melanocyte precursors in the neural crest. *Developmental Biology*, 153, 396-401, 1992.
39. Alexander, W.S., **Lyman, S. D.**, and Wagner, E.F. Expression of functional c-kit receptors rescues the genetic defect of *W* mutant mast cells. *EMBO J.* 10, 3683-3691, 1991.
40. Beckmann, M.P., Munger, W.E., Kozlosky, C., VandenBos, T., Price, V., **Lyman, S. D.**, Gerard, N. P., Gerard, C., and Cerretti, D. P. Molecular characterization of the interleukin-8 receptor. *Biochem. Biophys. Res. Comm.* 179, 784-789, 1991.
41. Williams, D. E. and **Lyman, S. D.** Molecular and cellular biology of mast cell growth factor: The gene product of the murine Steel locus. *Behring Institute Mitt.* 90, 23-27, 1991.
42. Tsuji, K., **Lyman, S.D.**, Sudo, T., Clark, S.C., and Ogawa, M. Enhancement of murine hemopoiesis by synergistic interactions between steel factor (ligand for c-kit), interleukin 11, and other early-acting factors in culture. *Blood* 79, 2855-2860, 1992.
43. Williams, D. E., de Vries, P., Namen, A.E., Widmer, M.B., and **Lyman, S.D.** The Steel factor. *Developmental Biol.* 151, 368-376, 1992.
44. Brannan, C.I., Bedell, M.A., Resnick, J.L., Eppig, J.J., Handel, M.A., Williams, D.E., **Lyman, S.D.**, Donovan, P.J., Jenkins, N.A., and Copeland, N.G. Developmental abnormalities in Steel^{17H} mice result from splicing defect in the steel factor cytoplasmic tail. *Genes and Development* 6, 1832-1842, 1992.
45. Zakut, R., Perlis, R., Eliahu, S., Yarden, Y., Givol, D., **Lyman, S.D.**, and Halaban, R. Kit ligand inhibits the growth of kit expressing melanoma cells. *Oncogene* 8, 2221-2229, 1993.
46. Hu, Q., Trevisan, M., Xu, Y., Dong, W., Berger, S., **Lyman, S.D.**, Williams, D.E., and Minden, M.D. The effect of murine c-kit on the leukaemogenic potential of 32D cells. *J. Clin. Invest.* 95, 2530-2538, 1995.
47. Williams, D. E. and **Lyman, S. D.** Biology of the Steel factor, pp.5-10, in Current Opinion in Hematology, John Adamson, (Ed.) Current Science, Philadelphia, PA , 1993.
48. **Lyman, S.D.**, James, L., Sleath, P.R., Zappone, J., Beckmann, M.P., and Bird, T. Characterization of the protein encoded by the *flt3(flk2)* receptor-like tyrosine kinase gene. *Oncogene* 8, 815-822, 1993.
49. **Lyman, S.D.**, James, L., VandenBos, T., de Vries, P., Brasel, K., Gliniak, B., Hollingsworth, L. T., Picha, K.S., McKenna, H.J., Splett, R.R., Fletcher, F.A., Maraskovsky, E., Farrah, T., Foxworth, D., Williams, D.E., and Beckmann, M.P. Molecular cloning of a ligand for the *flt3/flk-2* tyrosine kinase receptor - A proliferative factor for primitive hematopoietic cells. *Cell* 75, 1157-1167, 1993.
50. **Lyman, S.D.**, James, L., Johnson, L., Brasel, K., Escobar, S.S., Downey, H., de Vries, P., Splett, R.R., Beckmann, M.P., and McKenna, H. Cloning of the human homologue of the murine *flt3* ligand: A growth factor for early hematopoietic progenitor cells. *Blood* 83, 2795-2801, 1994.

51. **Lyman, S.D.**, James, L., Escobar, S., Downey, H., de Vries, K., Brasel, K., Stocking, K., Beckmann, M.P., Copeland, N.G., Cleveland, L.S., Jenkins, N.A., and Davison, B. Identification of soluble and membrane bound isoforms of the murine flt3 ligand generated by alternative splicing of mRNAs. *Oncogene* 10, 149-157, 1995.
52. **Lyman, S.D.**, Brasel, K., Rousseau, A.-M., and Williams, D.E. The flt3 ligand: A hematopoietic stem cell factor whose activities are distinct from steel factor. *Stem Cells* 12, 99-110, 1994.
53. **Lyman, S.D.** and Williams, D.E. Biology and Potential Clinical Applications of flt3 ligand. *Current Opinion in Hematology* 2, 177-181, 1995.
54. **Lyman, S.D.**, Stocking, K., Davison, B. Fletcher, F., Johnson, L., and Escobar, S.S. Structural analysis of human and murine flt3 ligand genomic loci. *Oncogene* 11, 1165-1172, 1995.
55. **Lyman, S.D.** Biology of flt3 ligand and receptor. *Int. J. Hematol.* 62, 63-73, 1995.
56. Beckmann, M.P., Cerretti, D.P., Baum, P., VandenBos, T., James, L., Farrah, T., Kozlosky, C., Hollingsworth, T., Shilling, H., Maraskovsky, E., Fletcher, F., Lhotak, V., Pawson, T., and **Lyman, S.D.** Molecular characterization of a family of ligands for eph-related tyrosine kinase receptors. *EMBO J.* 13, 3757-3762, 1994.
57. Fletcher, F.A., Renshaw, B., Hollingsworth, T., Baum, P., **Lyman, S.D.**, Jenkins, N.A., Gilbert, D.J., Copeland, N.G., and Davison, B.L. Genomic organization and chromosomal localization of mouse Eplg2, a gene encoding a binding protein for the receptor tyrosine kinase elk. *Genomics* 24, 127-132, 1994.
58. Fletcher, F.A., Carpenter, M., Shilling, H., Baum, P., Ziegler, S., Gimpel, S., Hollingsworth, T., Vanden Bos, T., James, L., Hjerrild, K., Davison, B.L., **Lyman, S.D.**, and Beckmann, M.P. LERK-2, a binding-protein for the receptor-tyrosine kinase ELK, is evolutionarily conserved and expressed in a developmentally regulated pattern. *Oncogene* 9, 3241-3247, 1994.
59. Kozlosky, C.J., Maraskovsky, E., McGrew, J.T., VandenBos, T., Teepe, M., **Lyman, S.D.**, Srinivasan, S., Fletcher, F., Gayle, R., Cerretti, D.P., and Beckmann, M.P. Ligands for the Receptor Tyrosine Kinases Hek and Elk: Isolation of cDNAs encoding a family of ligands. *Oncogene*, 10, 299-306, 1995.
60. Fletcher, F.A., Huebner, K., Shaffer, L.G., Fairweather, N.D., Monaco, A.P., Muller, U., Druck, T., Simoneaux, D., Chelly, J., Belmont, J.W., Beckmann, M.P., and **Lyman, S.D.** Assignment of the gene (EPLG2) encoding a high-affinity binding protein for the receptor Tyrosine Kinase elk to a 200-kilobasepair region in human chromosome Xq12. *Genomics* 25, 334-335, 1995.
61. Broxmeyer, H.E., Lu, L., Cooper, S., Ruggieri, L., Li, Z.-H., and **Lyman, S.D.** Flt3 ligand stimulates/costimulates the growth of myeloid stem/progenitor cells. *Exp. Hematol.* 23, 1121-1129, 1995.
62. Hirayama, F., **Lyman, S.D.**, Clark, S.C., and Ogawa, M. The flt3 ligand supports proliferation of lymphohemopoietic progenitors and early B-lymphoid progenitors. *Blood* 85, 1762-1768, 1995.

63. Jacobsen, S.E.W., Okkenhaug, C., Myklebust, J., Veiby, O.P., and **Lyman, S.D.** The flt3 ligand potently and directly stimulates the growth and expansion of primitive murine bone marrow cells in vitro: Synergistic interactions with Interleukin (IL) 11, IL-12, and other hematopoietic growth factors. *J. Exp. Med.*, 181, 1357-1363, 1995.
64. Jacobsen, S.E.W., Veiby, O.P., Myklebust, J., Okkenhaug, C., and **Lyman, S.D.** Ability of flt3 ligand to stimulate the in vitro growth of primitive murine hematopoietic progenitors is potently and directly inhibited by transforming growth factor- β and tumor-necrosis factor- α . *Blood*, 87, 5016-5026, 1996.
65. Rusten, L.S., **Lyman, S.D.**, Veiby, O.P., and Jacobsen, S.E.W. The flt3 ligand is a direct and potent stimulator of the growth of primitive and committed human CD34⁺ bone marrow progenitor cells in vitro. *Blood* 87, 1317-1325, 1996.
66. Veiby, O.P., Jacobsen, F.W., Cui, L., **Lyman, S.D.**, and Jacobsen, S.E.W. The flt3 Ligand promotes the survival of primitive hematopoietic progenitor cells with myeloid as well as B-lymphoid potential: suppression of apoptosis and counteraction by TNF- α and TGF- β . *J. Immunol.* 157, 2953-2960, 1996.
67. McKenna, H.J., de Vries, P., Brasel, K., **Lyman, S.D.**, and Williams, D.E. Effect of flt3 ligand on the ex vivo expansion of human CD34⁺ hematopoietic progenitor cells. *Blood* 86, 3413-3420, 1995.
68. Brasel, K., Escobar, S., Anderberg, R., de Vries, P., Gruss, H.-J., and **Lyman, S.D.** Expression of the flt3 receptor and its ligand on hematopoietic cells. *Leukemia* 9, 1212-1218, 1995.
69. Gabbianelli, M., Pelosi, E., Montesoro, E., Valtieri, M., Lucheti, L., Samoggia, P., Vitelli, L., Barberi, T., Testa, T., **Lyman, S.D.**, and Peschle, C. Multi-level effects of flt3 ligand on human hematopoiesis: expansion of putative stem cells and proliferation of granulomonocytic progenitors/monocytic precursors. *Blood* 86, 1661-1670, 1995.
70. **Lyman, S.D.**, Seaberg, M., Hanna, R., Abkowitz, J.L., Prechal, J., Schultz, J., and Shahidi, N.T. Plasma/serum levels of Flt3 ligand are low in normal individuals and are highly elevated in patients with Fanconi anemia and acquired aplastic anemias. *Blood* 86, 4091-4096, 1995.
71. Eder, M., Hemmati, P., Kalina, U., Ottmann, O.G., Hoelzer, D., **Lyman, S.D.**, and Ganser, A. Effects of flt3 ligand and interleukin-7 on in vitro growth of acute lymphoblastic leukemia cells. *Exp. Hematology* 24, 371-377, 1996.
72. Ray, R.J., Paige, C.J., Furlonger, C., **Lyman, S.D.**, and Rottapel, R. Flt3 ligand supports the differentiation of early B cell progenitors in the presence of Interleukin-11 and Interleukin-7. *Eur. J. Immunol.* 26, 1504-1510, 1996.
73. Cerretti, D.P., **Lyman, S.D.**, Kozlosky, C.J., Copeland, N.G., Gilbert, D.J., Jenkins, N., Valentine, V., Kirstein, M.N., Shapiro, D.N., and Morris, S.W. The genes encoding the eph-related receptor tyrosine kinase ligands LERK-1 (*EPLG1*, *Epl1*), LERK-3 (*EPLG3*, *Epl3*), and LERK-4 (*EPLG4*, *Epl4*) are clustered on human chromosome 1 and mouse chromosome 3. *Genomics* 33, 277-282, 1996.

74. McKenna, H.J., Smith, F.O., Brasel, K., Hirschstein, D., Bernstein, I.D., **Lyman, S.D.**, and Williams, D.E. Effects of flt3 ligand on acute myeloid and lymphocytic leukemic blast cells from children. *Exp. Hematol.* 24, 378-385, 1996.
75. Fujimoto, K., **Lyman, S.D.**, Hirayama, F., and Ogawa, M. Isolation and characterization of primitive hematopoietic progenitors of murine fetal liver. *Exp. Hematol.* 24, 285-290, 1996.
76. Williams, D.E., and **Lyman, S.D.** Steel factor, in Human Cytokines: Handbook for Basic and Clinical Research, Vol. 2, pp. 316-330, Edited by B.B. Aggarwal and J.U. Gutterman, Blackwell Science Press, Boston, 1996.
77. Broxmeyer, H.E., Cooper, S., Etienne-Julan, M., Braun, S., Lu, L., **Lyman, S.D.**, and Srivastava, A. Cord blood hematopoietic stem/progenitor cell growth and gene transduction using adeno-associated and retroviral vectors. Ontogeny of Hematopoiesis (Proceedings of the colloquium on "Foetal and neonatal hematopoiesis and the mechanisms of bone marrow failure". John Libbey Eurotext Limited, Montrouge, France) 235, 109-114, 1995.
78. Ohishi, K., Katayama, N., Itoh, R., Mahmud, N., Miwa, H., Kita, K., Minami, N., Shirakawa, S., **Lyman, S.D.**, and Shiku, H. Accelerated cell cycling of hematopoietic progenitors by the flt3 ligand that is modulated by transforming growth factor- β . *Blood* 87, 1718-1727, 1996.
79. Takahira, H., **Lyman, S.D.**, and Broxmeyer, H.E. Flt3 ligand prolongs survival of CD34⁺⁺⁺ human umbilical cord blood myeloid progenitors in serum-depleted culture medium. *Ann. Hematol.* 72, 131-135, 1996.
80. Lisovsky, M., Braun, S.E., Ge, Y., Takahira, H., Lu, L., Savchenko, V.G., **Lyman, S.D.**, and Broxmeyer, H.E. Flt3 ligand production by human bone marrow stromal cells. *Leukemia* 10, 1012-1018, 1996.
81. Veiby, O.P., **Lyman, S.D.**, and Jacobsen, S.E.W. Combined signaling through interleukin-7 receptors and flt3 but not c-kit potently and selectively promotes B-cell commitment and differentiation from uncommitted murine bone marrow progenitor cells. *Blood* 88, 1256-1265, 1996.
82. Hjertson, M., Sundstrom, C., **Lyman, S.D.**, Nilsson, K., and Nilsson, G. Stem cell factor, but not flt3 ligand, induces differentiation and activation of human mast cells. *Exp. Hematol.* 24, 748-754, 1996.
83. McKenna, H.J. and **Lyman, S.D.** Biology of flt3 ligand, a novel regulator of hematopoietic stem and progenitor cells. in Bone Marrow Transplantation: Basic and Clinical Studies. (Ikehara, S., Takaku, F. and Good, R.A. editors). Springer-Verlag Tokyo, 85-93, 1996.
84. Wodnar-Filipowicz, A., **Lyman, S.D.**, Gratwohl, A., Tichelli, A., Speck, B., and Nissen, C. Flt3 ligand level reflects hematopoietic progenitor cell function in aplastic anemia and chemotherapy-induced bone marrow aplasia. *Blood* 88, 4493-4499, 1996.
85. Maraskovsky, E., Brasel, K., Teepe, M., Roux, E., **Lyman, S.D.**, Shortman, K.D., and McKenna, H.J. Dramatic increase in the numbers of functionally mature dendritic cells in Flt3 ligand-treated mice: multiple dendritic cell subpopulations identified. *J. Exp. Med.* 184, 1953-1962, 1996.

86. Turner, A.M., Lin, N.L., Issarachai, S., **Lyman, S.D.**, and Broudy, V. FLT3 receptor expression on the surface of normal and malignant human hematopoietic cells. *Blood* 88, 3383-3390, 1996.
87. Ramsfjell, V., Borge, O.J., Veiby, O.P., Cardier, J., Murphy Jr., M.J., **Lyman, S.D.**, Lok, S., and Jacobsen, S.E.W. Thrombopoietin, but not erythropoietin, directly stimulates multilineage growth of primitive murine bone marrow progenitor cells in synergy with early acting cytokines: Distinct interactions with the ligands for *c-kit* and FLT3. *Blood* 88, 4481-4492, 1996.
88. Brasel, K., McKenna, H.J., Morrissey, P.J., Charrier, K., Morris, A.E., Lee, C.C., Williams, D.E., and **Lyman, S.D.** Hematologic effects of flt3 ligand in vivo in mice. *Blood* 88, 2004-2012, 1996.
89. Ku, H., Hirayama, F., Kato, T., Miyazaki, H., Aritomi, M., Ota, Y., D'Andrea, A., **Lyman, S.D.**, and Ogawa, M. Soluble thrombopoietin receptor (mpl) and granulocyte colony-stimulating factor receptor directly stimulate proliferation of primitive hematopoietic progenitors of mice in synergy with Steel factor or the ligand for flt3/flk2. *Blood*, 88, 4124-4131, 1996.
90. Cerretti, D.P., VandenBos, T., Nelson, N., Kozlosky, C.J., Reddy, P., Maraskovsky, E., Park, L.S., **Lyman, S.D.**, Copeland, N.G., Gilbert, D.J., Jenkins, N.A., and Fletcher, F.A. Isolation of LERK-5: A ligand of the eph-related receptor tyrosine kinases. *Mol. Immunol.* 32, 1197-1205, 1995.
91. Braun, S.E., Aronica, S.M., Ge, Y., Takahira, H., Etienne-Julan, M., Lu, L., Minden, M., **Lyman, S.D.**, and Broxmeyer, H.E. Retroviral mediated gene transfer of Flt3 Ligand enhances proliferation and MAP kinase activity of AML5 cells. *Exp. Hematol.* 25, 51-56, 1997.
92. Huang, S., Luca, M., Gutman, M., McConkey, D.J., Langley, K.E., **Lyman, S.D.**, and Bar-Eli, M. Enforced c-kit expression renders highly metastatic human melanoma cells susceptible to stem cell factor-induced apoptosis and inhibits their tumorigenic and metastatic potential. *Oncogene* 13, 2339-2347, 1996.
93. Ohmizono, Y., Sakabe, H., Kimura, T., Tanimukai, S., Matsumura, T., **Lyman, S.D.**, and Sonoda, Y. Thrombopoietin augments ex vivo expansion of human cord blood derived hematopoietic progenitors in combination with stem cell factor and flt3 ligand. *Leukemia* 11, 524-530, 1997.
94. Yonemura, Y., Ku, H., **Lyman, S.D.**, and Ogawa, M. In vitro expansion of hemopoietic progenitors and maintenance of stem cells: Comparison between flt3/flk-2 ligand and kit ligand. *Blood* 89, 1915-1921, 1997.
95. Sonoda, Y., Kimura, T., Sakabe, H., Tanimukai, S., Ohmizono, Y., Nakagawa, S., Yokota, S., **Lyman, S.D.**, and Abe, T. Human flt3 ligand acts on myeloid as well as multipotential progenitors derived from purified CD34⁺ blood progenitors expressing different levels of c-kit protein. *Eur. J. Haematol.* 58, 257-264, 1997.
96. Papayannopoulou, T., Nakamoto, B., Andrews, R.G., **Lyman, S.D.**, and Lee, M.Y. In vivo effects of flt3/flk-2 ligand on mobilization of hemopoietic progenitors in primates and potent synergistic enhancement with Granulocyte Colony-Stimulating Factor. *Blood* 90, 620-629, 1997.

97. Wodnar-Filipowicz, A., Chklovskaya, E., Manz, C.Y., **Lyman, S.D.**, and Nissen, C. Effect of flt3 ligand on in vitro growth and expansion of colony-forming bone marrow cells from patients with aplastic anemia. *Exp. Hematol.* 25, 573-581, 1997.
98. Strobl, H., Bello-Fernandez, C., Riedl, E., Pickl, W.F., Majdic, O., **Lyman, S.D.**, and Knapp, W. Flt3 ligand in cooperation with Transforming Growth Factor- β potentiates in vitro development of Langerhans-type dendritic cells and allows single-cell dendritic cell cluster formation under serum-free conditions. *Blood* 90, 1425-1434, 1997.
99. Chen, K., Braun, S., **Lyman, S.**, Fan, Y., Traycoff, C.M., Wiebke, E.A., Gaddy, J., Sledge, G., Broxmeyer, H.E., and Cornetta, K. Antitumor activity and immunotherapeutic properties of flt3-ligand in a murine breast cancer model. *Cancer Res.* 57, 3511-3516, 1997.
100. Dougher, M., Torley, L., Wasserstrom, H., Shridaran, L., Westdock, P., Hileman, R.E., Fromm, J.R., Anderberg, R., **Lyman, S.**, Linhardt, R.J., Kaplan, J., and Terman, B.I. Identification of a heparin binding peptide on the extracellular domain of the KDR VEGF receptor. *Growth Factors* 14, 257-268, 1997.
101. Brasel, K., McKenna, H.J., Charrier, K., Morrissey, P.J., Williams, D.E., and **Lyman, S.D.** Flt3 ligand synergizes with Granulocyte-Macrophage Colony-Stimulating Factor or Granulocyte Colony-Stimulating Factor to mobilize hematopoietic progenitor cells into the peripheral blood of mice. *Blood* 90, 3781-3788, 1997.
102. Dooley, D.C., Xiao, M., Oppenlander, B.K., Plunkett, J.M., and **Lyman, S.D.** Flt3 ligand enhances the yield of primitive cells after ex vivo cultivation of CD34⁺ CD38^{dim} cells and CD34⁺ CD38^{dim} CD33^{dim} HLA-DR⁺ cells. *Blood* 90, 3903-3913, 1997.
103. Bello-Fernandez, C., Matyash, M., Strobl, H., Pickl, W.F., Majdic, O., **Lyman, S.D.**, and Knapp, W. Efficient retrovirus-mediated gene transfer of dendritic cells generated from CD34⁺ cord blood cells under serum-free conditions. *Human Gene Therapy* 8, 1651-1658, 1997.
104. Veiby, O.P., Borge, O.J., Martensson, A., Beck, E.X., Schade, A.E., Grzegorzewski, K., **Lyman, S.D.**, Martensson, I.-L., and Jacobsen, S.E.W. Bidirectional effect of Interleukin-10 on early murine B-cell development: Stimulation of flt3-ligand plus Interleukin-7-dependent generation of CD19⁺ proB cells from uncommitted bone marrow progenitor cells and growth inhibition of CD19⁺ proB cells. *Blood* 90, 4321-4331, 1997.
105. Ebihara, Y., Tsuji, K., **Lyman, S.D.**, Sui, X., Yoshida, M., Muraoka, K., Yamada, K., Tanaka, R., and Nakahata, T. Synergistic action of flt3 and gp130 signalings in human hematopoiesis. *Blood* 90, 4363-4368, 1997.
106. Buhring, H.-J., Birnbaum, D., Brasel, K., Civin, C., Gotze, K., **Lyman, S.D.**, Rappold, I., and Rosnet, O. CD135 (FLT3/FLK2/STK-1) Workshop Panel Report in *Leukocyte Typing VI* (Ed. by T. Kishimoto et al) pp. 875-879, Garland Publishing, Inc. New York, 1997.
107. Maraskovsky, E., Pulendran, B., Brasel, K., Teepe, M., Roux, E. R., Shortman, K., **Lyman, S.D.**, McKenna, H. Dramatic numerical increase of functionally mature dendritic cells in flt3 ligand-treated mice. *J. Adv. Exp. Med. Biol.*, 417 (*Dendritic Cells in Fundamental and Clinical Immunology*, Vol. 3), 33-40, 1997.

108. Kobayashi, M., Laver, J.H., **Lyman, S.D.**, Kato, T., Miyazaki, H., and Ogawa, M. Thrombopoietin, steel factor and the ligand for flt3/flk2 interact to stimulate the proliferation of human hematopoietic progenitors in culture. *Int. J. Hematol.* 66, 423-434, 1997.
109. **Lyman, S.D.**, Maraskovsky, E., and McKenna, H.J. Flt3 ligand, in The Cytokine Handbook, 3rd Edition, Angus Thomson, Editor, Academic Press, pp. 727-752, 1998.
110. **Lyman, S.D.**, Mire-Sluis, A. and Gliniak, B. The Steel Factor/kit Ligand/Stem Cell Factor, in Cytokines, A. Mire-Sluis and R. Thorpe, Editors, Academic Press, pp. 297-320, 1998.
111. **Lyman, S.D.** and Jacobsen, S.E.W. *c-kit* Ligand and flt3 Ligand: Stem/progenitor cell factors with overlapping yet distinct activities. *Blood* 91, 1101-1134, 1998.
112. Strockbine, L.D., Cohen, J.I., Farrah, T., **Lyman, S.D.**, Wagener, F., DuBose, R., Armitage, R.J., and Spriggs, M.K. The Epstein-Barr virus BARF1 gene encodes a novel, soluble Colony-Stimulating Factor-1 receptor. *J. Virol.* 72, 4015-4021, 1998.
113. Slanicka Krieger, M., Nissen, C., Manz, C.Y., Toksoz, D., **Lyman, S.D.**, and Wodnar-Filipowicz, A. The membrane-bound isoform of stem cell factor synergizes with soluble flt3 ligand in supporting early hematopoietic cells in long-term cultures of normal and aplastic anemia bone marrow. *Exp. Hematol.* 26, 365-373, 1998.
114. Sakabe, H., Kimura, T., Tanimukai, S., Ohmizono, Y., Yokota, S., Hodohara, K., Okuda, T., Abe, T., **Lyman, S.D.**, and Sonoda, Y. Haematopoietic action of flt3 ligand on cord blood-derived CD34-positive cells expressing different levels of flt3 or c-kit tyrosine kinase receptor: Comparison with stem cell factor. *Eur. J. Haematol.* 60, 297-306, 1998.
115. Graddis, T.J., Brasel, K., Friend, D., Srinivasan, S., **Lyman, S.D.**, March, C.J., and McGrew, J.T. Structure-function analysis of human flt3 ligand-flt3 receptor interactions using a rapid functional screen. *J. Biol. Chem.* 273, 17626-17633, 1998.
116. **Lyman, S.D.** Biologic effects and potential clinical applications of flt3 ligand. *Current Opinion in Hematology* 5, 192-196, 1998.
117. Gratwohl, A., John, L., Baldomero, H., Roth, J., Tichelli, A., Nissen, C., **Lyman, S.D.**, and Wodnar-Filipowicz, A. Flt-3 ligand provides hematopoietic protection from total body irradiation in rabbits. *Blood* 92, 765-769, 1998.
118. Hawley, T.S., Fong, A.Z.C., Griesser, H., **Lyman, S.D.**, and Hawley, R.G. Leukemic predisposition of mice transplanted with gene-modified hematopoietic precursors expressing flt3 ligand. *Blood* 92, 2003-2011, 1998.
119. Balduini, A., Braun, S.E., Cornetta, K., **Lyman, S.D.**, and Broxmeyer, H. Comparative effects of retroviral mediated gene transfer into primary human stromal cells of flt3 ligand, IL-3, and GM-CSF on production of cord blood progenitor cells in long term culture. *Stem Cells* 16, 37-49, 1999.
120. Pless, M., Wodnar-Filipowicz, A., John, L., Baldomero, H., **Lyman, S.D.**, Nissen, C., and Gratwohl, A. Synergy of growth factors during mobilization of peripheral blood precursor cells with

recombinant human flt3-ligand and Granulocyte Colony-Stimulating Factor in rabbits. *Exp. Hematology* 27, 155-161, 1998.

121. Chklovskaya, E., Jansen, W., Nissen, C., **Lyman, S.D.**, Rahner, C., Landmann, L., Wodnar-Filipowicz, A. Mechanism of Flt3 ligand expression in bone marrow failure: translocation from intracellular stores to the surface of T lymphocytes following chemotherapy-induced suppression of hematopoiesis. *Blood* 93, 2595-2604, 1999.

122. Zwierzina, H., Anderson, J.E., Rollinger-Holzing, I., Torok-Storb, B., Nuessler, V., and **Lyman, S.D.** Endogenous flt3 ligand serum levels are associated with disease stage in patients with myelodysplastic syndromes. *Leukemia* 13, 553-557, 1999.

123. Banu, N., Deng, B., **Lyman, S.D.**, and Avraham, H. Modulation of hematopoietic progenitor development by flt-3 ligand. *Cytokine* 11, 679-688, 1999.

124. **Lyman, S.D.**, Escobar, S., Rousseau, A.-M., Armstrong, A., and Fanslow, W.C. Identification of CD7 as a cognate of the human K12 (SECTM1) protein. *J. Biol. Chem.* 275, 3431-3437, 2000.

125. McKenna, H.J., Stocking, K., Miller, B., Brasel, K., De Smedt, T., Maraskovsky, E., Maliszewski, C., Lynch, D., Smith, J., Pulendran, B., Roux, E., Teepe, M., **Lyman, S.D.**, and Peschon, J. Mice lacking flt3 ligand have deficient hematopoiesis affecting hematopoietic progenitor cells, dendritic cells, and natural killer cells. *Blood* 95, 3489-3497, 2000.

126. Maraskovsky, E., **Lyman, S.D.**, Maliszewski, C.R., and Lynch, D.H. Flt-3 and Flt-3 ligand, in *Principles and Practice of the Biologic Therapy of Cancer*, 3rd Edition., Steven Rosenberg, Ed. Lipincott, Williams, and Wilkins, Philadelphia, 875-889, 2000.

127. Pfister, O., Chklovskaya, E., Jansen, W., Meszaros, K., Nissen, C., Rahner, C., Hurwitz, N., Bogatcheva, N., **Lyman, S.D.**, and Wodnar-Filipowicz, A. Chronic overexpression of membrane-bound flt3 ligand by T lymphocytes in severe aplastic anemia. *Br. J. Haematol.* 109, 211-220, 2000.

128. Quentmeier, H., Drexler, H.G., Fleckenstein, D., Zaborski, M., Armstrong, A., Sims, J., and **Lyman, S.D.** Cloning of human thymic stromal lymphopoietin (TSLP) and signaling mechanisms leading to proliferation. *Leukemia* 15, 1286-1292, 2001.

129. **Lyman, S.D.**, and McKenna, H.J. Flt3 ligand, in The Cytokine Handbook, 4th Edition. Angus Thomson, Editor, Academic Press, Volume 2, pp. 989-1010, 2003.

EXHIBIT B

GAP of: p75-P20333 check: 5724 from: 1 to: 461

p75(smith)

to: p75-EP939121 check: 2507 from: 1 to: 392

p75(EP939121)

Symbol comparison table: /apps/gcg/gcgcore/data/rundata/blosum62.cmp
CompCheck: 1102

Gap Weight:	8	Average Match:	2.778
Length Weight:	2	Average Mismatch:	-2.248
Quality:	2052	Length:	462
Ratio:	5.235	Gaps:	1
Percent Similarity:	98.977	Percent Identity:	98.977

Match display thresholds for the alignment(s):

```

| = IDENTITY
: = 2
. = 1

```

p75-P20333 x p75-EP939121 April 12, 2007 13:55 ..

```

      .
      .
      .
51 qmccskcspgqhakvfctktsdtvcdscdestyqlwnwvpeclscgsr 100
      |||||||||||||||||||||||||||||||||||||||
1 .....SDSVCDSCDESTYQLWNWVPECLSCGSRC 30
101 ssdqvetaactreqnricrprgwygalskqegcrlcaplrkcrpgfgva 150
      |||||||||||||||||||||||||||||||||||||||
31 SSDQVETAQACTREQNRICRPRGWCALSKQEGCRLCAPLPKCRPGFGVA 80
151 rpgtetsdvvckpcapgtfsnttsttdicrphqicnvvaipgnasmdavc 200
      |||||||||||||||||||||||||||||||||||||||
81 RPGTETSDVVCKPCAPGTFSNTTSTTDICRPHQICNVVAIPGNASRDAVC 130
201 tstsptsrmapgavhlpqpvrstrqhtaptpepstapstsfllpmgsp 250
      |||||||||||||||||||||||||||||||||||||||
131 TSTSPTSRMAPGAVHLPQPVSTRSQHTQPSPEPSTAPSTSFLLPMGSP 180
251 aegstgdfalpvglivgvtalgliliigvncvintqvkkkplclqreakv 300
      |||||||||||||||||||||||||||||||||||||||
181 AEGSTGDFALPVGLIVGVGTALGLLIIGVNCVINTQVKKKPLCLQREAKV 230

```

```
301 phlpadkargtqgpeqqhllitapsssssslessasaldraptrnqpqa 350
|||||
231 PHLPADKARGTQGPEQQHLLITAPSSSSSSLESSASALDRRAPTRNQPQA 280
|||||
351 pgveasgagearastgss.dsppgghgtqvnvtcivnvcsssdhssqcscs 399
|||||
281 PGVEASGAGEARASTGSSADSSPGGHGTQVNVTCIVNVCSSSDHSSQCSCS 330
|||||
400 qasstmgdtddsspsespkdqvpfskeecafsrqletpetllgsteekpl 449
|||||
331 QASSTMGDTDDSSPSESPKDEQVPFSKEECAFRSQLETPETLLGSTEELPL 380
|||||
450 plgvpdagmkps 461
|||||
381 PLGVPDAGMKPS 392
```